Summary Statement for the ALS Cognitive-Frontotemporal Dementia (FTD) Subgroup

We have identified a group of cognitive and behavioral instruments which should be considered for ALS studies and which are appropriate for self-administration or for administration by health care providers who are not formally trained as psychologists or neuropsychologists. These instruments do not constitute definitive diagnostic assessments for behavioral and cognitive dysfunction, but rather serve as tools available for use by members of a typical ALS health care professional team (physicians, nurses, therapists, social workers). These measures can assist in determining whether an individual demonstrates sufficient cognitive and/or behavioral dysfunction to warrant further attention and investigation. More detailed descriptions of each measure follow this summary, and we hope they will be useful to help design the best combination of tests to fit the research or clinical purpose desired.

Table 1 summarizes the recommended instruments, highlighting the importance of adequate breadth of assessment, to include four clinical categories: cognition, behavior, depression, and pseudobulbar affect (PBA). The table also includes the administration time, availability, and whether each measure is ALS-specific.

We recommend that studies of cognition and behavior in ALS should include, at a minimum, one measure of cognition and one of behavior, selected from those classified as "Core" in Table 1. One screening measure of depression should also be strongly considered when assessing cognition and behavior. Finally, many studies of cognition and behavior can be augmented by using a measure for pseudobulbar affect. The Table denotes whether each measure constitutes a core, supplemental, or exploratory common data element (CDE), based on the NIH classification, with some minor modifications to make the classifications more specifically applicable to the cognitive and behavioral realm:

- Core: should be collected in all ALS studies of cognition and behavior
- Supplemental: important for some types of studies of cognition and behavior
- Exploratory: emerging or not yet validated but may have importance in the near future

Depending on the goals of a study, the importance of assessing all four domains may take priority over the CDE classification system when studying cognition and behavior.

The field of cognitive dysfunction in ALS is an evolving one, and many of the instruments described in this document are in the process of undergoing validation studies or additional development. A determination of whether to include an instrument in the Core, Supplemental, or Exploratory category was based not only on published validity studies, but on whether the instrument has been widely used by researchers in the ALS community, is in the process of being validated in the ALS population, or was considered to be particularly useful by an expert panel. Admittedly such recommendations are imperfect. We do not anticipate that these recommendations will be the final word in the field in a permanent sense, but rather we anticipate that these categories may change over time, and that instruments may be added to or removed from this list as additional data becomes available.

Table 1: List of Recommended Measures: ALS Cognitive-FTD CDE's

Name	CDE Classification*	Construct Measured†				ALS Specific (Yes/No)	Availability‡	Admin Time (min)
		C	B	D	PBA			
ALS Cognitive Behavioral Screen (ALS-CBS)	C	X	X			Y	PD	5-10
Abrahams Written Verbal Fluency	C	X				Y	A	15
Penn State Screen of Frontal and Temporal Dysfunction Syndromes (PSSFTS)	C	X	X			Y	A, C	20
UCSF Screen Battery	C	X	X	X	X	Y	A, C	45
Frontal Behavior Inventory (FBI)	C		X			N	A	15-25
Frontal Behavior Inventory-ALS Version (FBI-ALS)	S		X			Y	A	15-25
Frontal Behavior Inventory Modified by Heidler-Gary (FBI-Mod)	S		X			N	PD	10
Neuropsychiatric Inventory (NPI)	S		X			N	A	10-30
Neuropsychiatric Inventory-Clinician Version (NPI-C)	E		X			N	A	10-45
Neuropsychiatric Inventory-Questionnaire (NPI-Q)	S		X			N	A	10
Frontal Systems Behavior Scale (FrSBe)	S		X			N	C	10
Cambridge Behavioral Inventory-Revised (CBI-R)	S		X			N	A	15
Center for Neurologic Study- Lability Scale (CNS-LS)	S				X	N	A	5
Emotional Lability Questionnaire (ELQ)	S				X	Y	A	10-15
Beck Depression Inventory-II (BDI-II)	S			X		N	C	6
Geriatric Depression Scale (GDS)	E			X		N	PD	5
Hospital Anxiety and Depression Scale (HADS)	S			X		N	C	5
ALS Depression Inventory (ADI-12)	S			X		Y	PD	5
Hamilton Depression Rating Scale (HAM-D)	E			X		N	A	20-30

*CDE Classification: C = Core; S = Supplemental; E = Exploratory

†Construct Measured: C = cognition; B = behavior; D = depression; PBA = pseudobulbar affect

‡Availability: A = Author; PD = Public Domain; C = Copyrighted

Overview of Test Types

Cognitive-Behavioral Screening Exams

The ALS-CBS, the Penn State Screen, and the UCSF screen involve combinations of tests to create 5-minute, 20-minute, and 45-minute screening measures, respectively. Combination tests are perhaps the most useful to provide a more global assessment when time is limited. The ALS-CBS includes 8 cognitive tasks and a 15-item caregiver-rated behavioral questionnaire. It takes about 5 minutes to perform, is free, and is well validated. The UCSF screen battery (which uses the ALS-CBS), covers all 4 domains mentioned in the table and takes 45 minutes to perform. It is currently being used in the nationwide COSMOS study and validity data are being collected. The Penn State Screen Battery of Frontal and Temporal Dysfunction Syndromes (PSSFTS) takes 20 minutes and measures cognition, behavior, and intelligence. It is also being used in a multicenter study and validity data are being collected.

Cognitive measure

The only exclusively cognitive test discussed is the Abrahams Written Verbal Fluency test. This is a well-validated test which compensates for deficits in speaking and/or writing speed. It is very sensitive to cognitive impairment, specifically executive dysfunction, which is common in ALS.

Behavioral measures

The behavioral tests include, the Frontal Behavioral Inventory (FBI), the Neuropsychiatric Inventory (NPI), the Frontal Systems Behavior Scale (FrSBe), and the Cambridge Behavioral Inventory – Revised. There are several versions of the FBI and NPI; the advantages and disadvantages of each version are reviewed and discussed in detail in the following pages. With further validation, the FBI-ALS may be most promising since it is adjusted to avoid the confounders associated with symptoms of ALS versus FTD. The NPI-C is a promising new measure allowing greater flexibility to the clinician to use record review and clinical observation to document behavior change, which is particularly useful when caregiver-reporting lacks validity. The FrSBe is well validated and has been used in ALS studies. It takes 10 minutes to administer and additional time for scoring. The FrSBe is copyrighted, requiring purchase from the publisher. The Cambridge Behavioral Inventory – Revised is well-validated and time efficient due to the fact that the carer self-completes the measure. The CBI-R collapses the MND and FTD symptoms into one score. This feature makes it useful to capture both syndromes, but more difficult to disentangle them.

Depression and Pseudobulbar Affect

It is important to assess depression in ALS to ensure that it is not the cause of cognitive or behavioral dysfunction, or a confounding variable. Depression in the clinically significant range of Major Depressive Disorder is not pervasive in ALS populations, but nonetheless needs to be excluded. We reviewed the Beck Depression Inventory-II (BDI-II), the Geriatric Depression Scale (GDS), the Hamilton Depression Scale (HAM-D), the Hospital Anxiety and Depression Scale (HADS), and the ALS Depression Inventory (ADI-12). Each of these tests has pros and cons of length, time, and sensitivity. Depending on the situation, all could potentially be used in ALS studies, although the GDS has been validated on an older population and hence may not be suitable for younger ALS patients.

It is important to assess Pseudobulbar Affect (PBA) in ALS due to the availability to treatments (Elavil and the newly released drug Neudexta) and its potentially confounding affect on cognition and behavior. Two measures are discussed: the Center for Neurologic Study (CNS-LS) and the Emotional Lability Questionnaire (ELQ). Both scales are well validated but the ELQ was developed for ALS, allows ratings by carers, has a short version if no symptoms are present and a longer version if symptoms are present, making it perhaps more sensitive and easier to use in clinic.

More Extensive Assessments

There are many other instruments available for more extensive assessment of cognitive and behavioral function. These are generally chosen and administered by individuals with specialized neuropsychological training beyond that found in most ALS multidisciplinary clinics, and are therefore not within the domain of testing recommended by this subgroup. A particular shortcoming of these recommendations is that they lack any language instruments. Unfortunately, there is no valid, ALS-specific, short screening instrument for language, although there are longer, comprehensive assessments suitable for administration by neuropsychologists or language experts. As the field evolves, future revisions of this document will hopefully be able to incorporate one or more language instruments. A summary article[1] is recommended as a source for a description of additional measures. The article addresses comprehensive neuropsychological assessment in ALS patients across domains including but not limited to language, executive functioning, memory, visuospatial functioning, and intelligence.

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[1]Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lat Scler 2009;10:131-146.

Description of ALS-CBS for
ALS Common Data Elements

Instrument Name:	ALS Cognitive Behavioral Screen (ALS-CBS™)
Classification:	**Classification:** Core
Short Description of Instrument:	**Construct measured**: Frontal lobe cognitive dysfunction typical in ALS and behavioral changes associated with frontal lobe abnormalities. The test was designed as a screening tool to help identify patients most at risk for frontotemporal dementia (FTD) and rule out patients with minimal cognitive or behavioral change. **Generic vs. disease specific**: ALS-specific **Means of administration**: The screen can be completed in a routine clinical setting by any member of the care team, verbally or in writing. **Intended respondent**: Patient (cognitive section) and caregiver (behavioral questionnaire) **# of items**: The measure is composed of 8 cognitive tasks that examine changes in frontal lobe functioning, specifically attention, working memory, ocular function and verbal fluency. It also consists of an 15-item caregiver-rated behavioral change questionnaire. **# of subscales and names of sub-scales**: The cognitive section has 4 subscales: Attention (commands, mental addition/language, eye movements), Concentration (digits backwards), Tracking and Monitoring (months backwards, alphabet and letter-number alternation), and Initiation and Retrieval (F words). The behavioral section has one total score. **# of items per sub-scale:** Attention: 6 items, Concentration: up to 8 items, Tracking/Monitoring: 3 items, Initiation and Retrieval: 1 item.
Comments/Special instructions:	**Scoring:** The cognitive section results in a total score out of a possible 20 points. Scores are based both on accuracy and errors-made, the later of which result in deduction of points towards the total score. The behavioral section is a sum of the Likert scale items endorsed. **Background:** Developed as a screen to triage patients who required formal neuropsychological testing. Preliminary cut off scores may be useful to classify patients into subgroups of possible FTD, cognitively impaired, or cognitively normal.
References:	**Key Reference:** Woolley, SC, York, MK, Moore, DH, Strutt, AM, Murphy, J, Schulz, PE, Katz, JS. Detecting frontotemporal dysfunction in ALS: Utility of the ALS Cognitive Behavioral Screen (ALS-CBS™)**.** *Amyotrophic Lateral Sclerosis* 2010; 11(3): 303-311. **Other References:** Rush, B, Woolley, SC, Boylan, K. *Diagnostic Validity of the ALS Cognitive Behavioral Screen.* Amyotrophic Lateral Sclerosis 2010; 11 (Supp

	1): 33. Platform Presentation, 21st Int'l Symposium on ALS/MND, Orlando, FL.
Rationale/ Justification:	**Strengths:** Free to use and reproduce, easy to administer, relatively quick, does not require a neuropsychologist or M.D. for administration, can be completed either verbally or in writing, and many items can be completed with eye movements/augmentative communication. **Weaknesses:** Cannot provide a cognitive diagnosis, does not assess all cognitive domains (i.e. memory, confrontational naming, visuospatial functioning). **Psychometric Properties:** *Feasibility:* Easy to use, relatively short (5-10 minutes) *Reliability:* No reliability data published yet *Validity:* 100% accuracy for detecting ALS-FTD, Cognitively normal ALS patients can be distinguished from those with any cognitive deficit with 71% specificity and 85% sensitivity. The behavioral score predicts ALS-FTD with 80% sensitivity and 88% specificity. **Sensitivity to Change:** No published data regarding this. **Relationships to other variables:** Good sensitivity and specificity when compared to comprehensive neuropsychological test battery (gold standard) **Availability:** Contact Dr. Woolley via email: WoolleS@cpmcri.org for permission to use. **Purpose of Tool:** Screening **Used in:** Clinical trial, observational studies, clinical monitoring. **Administration time:** The screen takes approximately 5-10 minutes

Description of ADI-12™ for
ALS Common Data Elements

Instrument Name:	ALS Depression Inventory (ALS-12)
Classification:	**Classification:** Supplemental
Short Description of Instrument:	**Construct measured**: Depression in patients with ALS **Generic vs. disease specific**: ALS specific **Means of administration:** Paper and pencil or verbally **Intended respondent**: Patient **# of items**: 12, each rated on a 4-point Likert scale **# of subscales and names of sub-scales:** N/A. one total score **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** Total scores are generated by calculating a sum, ranging from 0-48. Higher scores suggest greater levels of depression. Scores greater than or equal to 23 suggest the need for further clinical assessment, and scores greater than or equal to 30 have 100% sensitivity to detect Major Depressive Disorder. **Background:** The ADI-12 was developed to assess depressive symptoms among patients with amyotrophic lateral sclerosis (ALS) by excluding items which may detect somatic or motor impairment occurring secondary to motor neuron degeneration and not depression. It is the only known depression screen developed specifically for this population.
References:	**Key Reference:** Hammer, EM, Hacker, S, Hautzinger, M, Meyer, TD, Kubler, A. Validity of the ALS Depression Inventory (ADI-12): A new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. *Journal of Affective Disorders 109:* 213-219, 2008. **Other References:** N/A
Rationale/ Justification:	**Strengths:** Short, easy to use and score, designed specifically for ALS patients. Does not assess motor or somatic symptoms which may otherwise skew results. Validity study used robust clinical assessment for comparison. **Weaknesses:** Not used in other studies to date so utility not widely known. **Psychometric Properties:** *Feasibility:* Easy to use, completed by patient *Reliability:* Unknown *Validity:* A cut-off of ≥30 (SE=100%, SP=83%) identified all patients with a current episode of major depression. A more liberal cut-off (≥23) identified all patients with any depressive disorder including minor depression at the cost of specificity (60%). **Sensitivity to Change:** Unknown

	Relationships to other variables: The correlation between the ADI-12 and the BDI was high (r=.81). **Availability:** Appears to be in the public domain **Purpose of Tool:** (Screening, diagnostic, etc) Screening **Used in:** Validation study **Administration time:** Approximately 5 minutes

Description of BDI-II for
ALS Common Data Elements

Instrument Name:	Beck Depression Inventory-II (BDI-II)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured:** This scale measures the existence and severity of symptoms of depression. **Generic vs. disease specific**: Generic **Means of administration:** Self-administered **Intended respondent:** Self-Report **# of items:** 21 items **# of subscales and names of sub-scales:** 2 subscales: Affective and Somatic subscales **# of items per sub-scale:** 8 for affective; 13 for somatic
Comments/Special instructions:	**Scoring:** Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. There is a four-point scale for each item ranging from 0 to 3. On two items (16 and 18) there are seven options to indicate either an increase or decrease of appetite and sleep. Cut-off score guidelines for the BDI-II are given with the recommendation that thresholds be adjusted based on the characteristics of the sample, and the purpose for use of the BDI-II. Total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe. **Background:** The BDI-II was developed in 1996 and was derived from the BDI. The 21-item survey is self-administered and is scored on a scale of 0-3 in a list of four statements arranged in increasing severity about a particular symptom of depression, bringing the BDI–II into alignment with DSM–IV criteria. The cutoffs used differ from the original scale: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms.
References:	**Key Reference:** Beck AT, Steer RA, Brown GK. *Manual for The Beck Depression Inventory Second Edition (BDI-II)*. San Antonio: Psychological Corporation; 1996. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess.* 1996; 67(3): 588-97. Steer RA, Ball R, Ranieri WF, Beck AT (January 1999). "Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients". *Journal of clinical psychology* **55** (1): 117–28. Storch EA, Roberti JW, Roth DA (2004). "Factor structure, concurrent validity,

	and internal consistency of the Beck Depression Inventory-Second Edition in a sample of college students". *Depression and anxiety* **19** (3): 187–9. **Other References:** Taylor L, Wicks P, Leigh PN, Goldstein LH. Prevalence of depression in amyotrophic lateral sclerosis and other motor disorders. *Eur J Neurol.* 2010; 17: 1047-1053. Rabkin JG, Albert SM, Del Bene ML, O'Sullivan MS, Tider T, Rowland LP, Mitsumoto H. Prevalence of depressive disorders and change over time in late-stage ALS. *Neurology* 2005; 65: 62-67. Trail M, Nelson ND, Van JN, Appel, Lai EC. A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression and their attitudes towards treatment options. *J Neurol Sci* 2003; 209(1-2):79-85
Rationale/ Justification:	**Strengths:** Easy to use, widely known, results easy to interpret. Item content improved over BDI-I to increase its correspondence with DSM-IV **Weaknesses:** Includes several items assessing physical symptoms which may be elevated in ALS patients due to motor neuron degeneration and not depression. However non-ALS clinical studies have provided evidence of the presence of at least two factors, a cognitive-affective factor and a somatic depressive symptom factor, which is more stable than in the BDI. However, this factor structure requires confirmation in ALS. **Psychometric Properties:** *Feasibility:* Easy to complete, relatively short compared to interview-based assessments. *Reliability:* 1 week test-retest stability is high (.93). Internal consistency (coefficient alpha) is .92-.94 depending on the sample. *Validity:* Construct validity was high when compared to the BDI (.93). **Sensitivity to Change:** Designed to assess mood within the most recent 2 week period, so comparison across assessments should reflect change over time. **Relationships to other variables:** BDI-II scores were not correlated with functional disability (ALSFRS-R scores) (Rabkin et al) in late-stage ALS patients, but did correlate with suffering, anger, perceived caregiver burden, weariness, and negative affect. In non-ALS studies, BDI-II scores correlate with measures of hopelessness, suicidal ideation and anxiety. **Availability:** Pearson- Assessment and Information. Beck Depression Inventory®–II (BDI®–II). http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8018-370&Mode=summary

Description of BDI-II for
ALS Common Data Elements

	http://www.sciencedirect.com/science/article/pii/S0165032707004181 **Purpose of Tool:** Screening for severity of depression **Used in:** Observational studies **Administration time:** 5 minutes, scoring 1 minute

Description of Cambridge Behavioural Inventory-Revised for ALS Common Data Elements

Instrument Name:	Cambridge Behavioural Inventory Revised (CBI-R)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured** : Cognitive Functioning, FTD-Type Behavioral and Personality Change, Activities of Daily Living, Mood Change **Generic vs. disease specific**: The measure is specific with regards to FTD-type dementia, but generic with regards to the presence of MND. It does not specify whether MND is present (e.g. specific clinical symptoms, progression issues, etc). **Means of administration**: Caregiver self-completes the questionnaire **Intended respondent**: Caregiver **# of items**: 45 **# of subscales and names of sub-scales**: Ten subscales: Memory and Orientation, Everyday Skills, Self-Care, Abnormal Behavior, Mood, Beliefs, Eating Habits, Sleep, Stereotypic and Motor Behaviors, Motivation **# of items per sub-scale**: 8, 5, 4, 6, 4, 3, 4, 2, 2, 2 and 5, respectively.
Comments/Special instructions:	**Scoring:** Items are scored according to the extent of the behavioral change: 0 = Never; 1 = A few times per month; 2 = A few times per week; 3 = Daily **Background:** The CBI-R is a global measure of change, capturing cognitive, physical, mood, sleep, and eating changes in addition to FTD-type behavior/personality change. The measure captures information about the level of functioning in the past month, and does not specify change across a period of time.
References:	**Key Reference:** Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? Amyotrophic Lateral Scler. 2011 Jan;12(1):45-51. Epub 2010 Sep 19. Wedderburn C, Wear H, Brown J, Mason SJ, Barker RA, Hodges J, Williams-Gray C. The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. J Neurol Neurosurg Psychiatry. 2008 May;79(5):500-3.
Rationale/ Justification:	**Strengths:** The measure can be completed by the caregiver without using staff time. It captures a distinct time period, in the past month, making it a useful tool for tracking change over time. **Weaknesses:** This measure collapses the MND and FTD symptoms into one score, thus not being able to separate out the behavioral/personality change from the MND-caused changes. This prevents the detection of ALS-normal patients from ALS-CI or ALS-FTD patients. When completed without staff clarification, caregivers can misinterpret items or fall into a pattern of

	responding (e.g. “patient is doing well”). **Psychometric Properties:** *Feasibility:* The measure is easy to use because it is a self-administered questionnaire. *Reliability:* No reliability studies found at this time. *Validity:* The CBI was found to be a valid instrument when compared with the Neuropsychiatric Inventory, PDQ-39 and UPDRS, with high internal consistency. The measure could distinguish between disease states, revealing distinct profiles for PD and other neurodegenerative diseases, including Huntington's disease, Alzheimer's disease and frontal variant frontotemporal dementia. **Sensitivity to Change:** The CBI has been found to be sensitive to changes in behaviour with disease progression. **Relationships to other variables:** This measure collapses many clinical constructs, yielding an overall functional score. It does not distinguish between cognitive and behavioral traits, depression, or MND disease progression. **Availability:** Author permission (John Hodges) is needed. **Purpose of Tool:** Screening. **Used in:** It can be used in any variety of investigations, including clinical trials. **Administration time:** 15 minutes.

Description of CNS-LS for
ALS Common Data Elements

Instrument Name:	Center for Neurologic Study Lability Scale (CNS-LS)
Classification:	**Classification:** Supplemental
Short Description of Instrument:	**Construct measured** : The CNS-LS measures affective lability in patients with ALS. **Generic vs. disease specific**: ALS-specific **Means of administration:** Self-completion **Intended respondent**: Patient **# of items**: 7 items **# of subscales and names of sub-scales:** 2- Labile laughter and labile tearfulness **# of items per sub-scale:** Labile laughter (4 items), labile tearfulness (3 items)
Comments/Special instructions:	**Scoring:** Each item is scored using a 5-point Likert scale, from 1 (applies never) 5 (applies most of the time) . **Background:** Pathological affect may occur in 27-49% of people with bulbar ALS. Devised to provide a short, self- report measure of affective lability in patients with ALS, to cover both labile tearfulness and laughter. Items were initially generated from interviews with patients identified as having affective lability and their caregivers.
References:	**Key Reference:** Moore SR, Gresham L, Bromberg MB, Kasarkis E, Smith RA (1997). A self report measure of affective lability. J. Neurol Neurosurg Psychiatry 1997;63:89-93. **Other References:** Brooks BR, Thisted RA, Appel SH, Bradley WG, Olney RK, Berg JE, Pope LE, and Smith RA (2004) Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine. A randomized trial. Neurology, 2004; 63:1364-1370
Rationale/ Justification:	**Strengths:** Subscales derived from principal components analysis **Weaknesses:** No proxy measure; only asks about the previous week; brief screen- no detailed information. **Psychometric Properties:** *Feasibility:* Easy to administer and score *Reliability:* Internal consistency: Cronbach's alpha laughter subscale = 0.91; Tearfulness subscale = 0.89 and Entire scale = 0.87 Test-retest reliability 0.88. *Validity:* CNS-LS total and subscale scores higher in patients identified by clinicians as showing meaningful symptoms of affective lability than in

those with few or no symptoms. Using a cut-off score of 11 for clinical purposes in predicting clinicians'diagnoses resulted in a sensitivity of 0.91 and specificity of 0.71. using a more stringent cut-off of 13 for research purposes gave a sensitivity of 0.84 and a specificity of 0.81 Smith et al 1997).

Change in CNS-LS scores correlated with decrease in episodes of laughing or crying (Brooks et al 2004)

Sensitivity to Change: Change in scores demonstrated in RCT comparing dextromethorphan hydrobromide/quinidine sulphate vs. dextromethorphan or quinidine (Brooks et al 2004)

Relationships to other variables: Total scores and Tearfulness subscale scores correlated with Beck Depression Inventory scores ($p<0.05$ and $p<0.01$ respectively) while Laughter scores did not.

Availability: Moore Sr, Gresham L, Bromberg MB, Kasarkis E, Smith RA (1997). A self report measure of affective lability. J. Neurol Neurosurg Psychiatry 1997;63:89-93.

www.nuedexta.com/pdf/**CNS**%20LS%20Questionnaire.pdf

Purpose of Tool: Screening, diagnostic, research

Used in: Clinical trial, observational study; also used in MS studies

Administration time: 5 minutes

Description of ELQ for
ALS Common Data Elements

Instrument Name:	Emotional Lability Questionnaire (ELQ)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured:** This questionnaire assesses frequency, duration of episodes, relation to external events, degree of voluntary control, congruence with mood state and subsequent distress of patients with pathological laughter and crying and emotional lability. **Generic vs. disease specific**: Disease specific **Means of administration:** Administered as a structured interview **Intended respondent**: Self-report by patient, proxy completion by caregiver in parallel version. **# of items**: 33 in total, (includes 3 screening questions) **# of subscales and names of sub-scales:** Laughing, Crying and Smiling **# of items per sub-scale:** 11 items
Comments/Special instructions:	**Scoring:** 4-point Likert scale - 0-3; proportional ratings, scale depending on question **Background:** Developed to provide detailed information for experimental investigation of nature and extent of emotional lability in the ALS population.
References:	**Key Reference:** Newsom-Davis IC, Abrahams S, Goldstein LH, Leigh PN. The emotional lability questionnaire: a new measure of emotional lability in amyotrophic lateral sclerosis. Journal of the neurological sciences 1999. 169(1-2):22-25. **Other References:** Palmieri A, Abrahams S, Soraru G, Mattiuzzi L, D'Ascenzo C, Pegoraro E, Angelini C. Emotional lability in MND; Relationship to cognition and psychopathology and impact on caregivers. J Neurol Sci 2009; 278:16-20 Wicks P, Abrahams S, Papps B, Al-Chalabi A, Shaw CE, Leigh PN, Goldstein LH SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. J Neurol 2009; 256: 234-241 Goldstein LH, Atkins L, Landau S, Brown R, Leigh PN Predictors of psychological distress in caregivers of people with amyotrophic lateral sclerosis: a longitudinal study. Psychological Medicine 2006; 36:1-11
Rationale/ Justification:	**Strengths:** Since episodes of pathological laughing and crying may occur with varying frequency this measure asks about the previous four weeks. Includes a scale for abnormal smiling. A carer/proxy version is available to allow for the fact that patients and carers may disagree about the frequency with which such episodes occur. Has also been validated in an Italian version.

Weaknesses: No validation against clinical diagnosis

Psychometric Properties:

Feasibility: Includes 3 screening questions which if answered negatively terminates the interview

Reliability: Cronbach's alpha for the Laughter scale= 0.8, Crying Scale =0.6. Test-retest reliability (4-6 week interval): intraclass correlation coefficients of 0.75 and 0.72 for Laughter and Crying Scales (Newsom-Davis 2004, Ph.D. Thesis)

Validity: Significant correlations between Crying and Total, Laughter and Total, Smiling and Total and Laughter and Smiling scores was significant at least $p<0.05$ (Newsom-Davis et al 1999). Statistically significant between self and independent ratings for Total scores, Crying scores and Laughter scores at least $p<0.05$ and also for Crying (self-rated) and Total (Independent-rater) (Newson-Davis et al 1999). Correlations between self- and independent rater versions for Total and Laughter scores significant at $p<0.001$(Palmieri et al 2009). Some evidence of ability to differentiate between ALS subtypes in comparison to controls (Wicks et al 2009).

Sensitivity to Change: No evidence of a significant change in scores over a six month period in ALS patients compared with controls (Abrahams et al., 2005)

Relationships to other variables: Self-rated Crying, Laughter and Total scores all correlated with bulbar impairment ($p<0.01$) (Newson-Davis et al 1999)**,** Total scores correlated with Total ALSFRS-R scores ($p<.01$) , ALSFRS-Language ($p<0.001$) and ALSFRS-Swallowing ($p<0.0001$) scores Laughing scores correlated with time since disease onset ($p<0.001$) (Palmieri et al, 2009); in addition, Total scores correlated with State anxiety (STAI Y1) scores ($p<0.01$)**;** Crying correlated with Emotional Fragility ($p<0.001$) and Beck Depression inventory scores ($p<0.001$) STAI Y ($p<0.01$) and Trait anxiety (STAI Y2) scores ($p<0.01$) (Palmieri et al, 2009). Total ELQ scores predictive of global measure of psychological distress in caregivers (Goldstein et al 2006). No correlation with cognitive performance (Palmieri et al. 2009).

Availability: From L.H. Goldstein or S Abrahams.

Purpose of Tool: Screening, diagnostic, research

Used in: Observational

Administration time: 10 -15 minutes (if responses to 3 screening questions negative then 1 min).

Description of FBI-ALS for
ALS Common Data Elements

Instrument Name:	Frontal Behavioral Inventory-ALS Version (FBI-ALS)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured :** FTD-Type Behavioral and Personality Change **Generic vs. disease specific:** ALS-specific and FTD specific **Means of administration**: Caregiver interview by research staff, by phone or in person, without patient present **Intended respondent**: Caregiver **# of items:** 24 **# of subscales and names of sub-scales:** Two subscales: Negative Behavior and Disinhibition **# of items per sub-scale:** 12 each
Comments/Special instructions:	**Scoring:** Items are scored according to the extent of the behavioral change: 0 = None/never; 1 = Mild, occasional; 2 = Moderate/often; 3 = Severe, most of the time. **Background:** This version of the FBI has one or two questions for each item, to help distinguish between MND symptoms and behavioral changes due to FTD. There are also instructions in parentheses to help disentangle the two. This effort to distinguish the physical MND from the behavioral/personality change makes this version ALS-specific yet lengthier as compared with the other two FBI versions.
References:	**Key Reference:** Murphy, Jennifer, at UCSF Dept of Neurology, in process of writing. **Other References: Original FBI references:** Kertesz, A., Davidson, W., & Fox, H. (1997). Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. Can J Neurol Sci, 24(1), 29-36. Kertesz, A. (1998). The quantification of behavior in frontal lobe dementia. In A. Kertesz & D. G. Munoz (Eds.), Pick's disease and Pick complex (pp. 47-67). New York: Wiley & Sons, Inc. Kertesz, A., Nadkarni, N., Davidson, W., & Thomas, A. W. (2000). The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. Journal of the International Neuropsychological Society, 6(4), 460-468. Kertesz, A., Davidson, W., McCabe, P., & Munoz, D. (2003). Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. Alzheimer Disease & Associated Disorders, 17(4), 223-229. Marczinski, C. A., Davidson, W., & Kertesz, A. (2004). A longitudinal study of

	behavior in frontotemporal dementia and primary progressive aphasia. Cogn Behav Neurol, 17(4), 185-190.
Rationale/ Justification:	**Strengths:** This ALS version of the FBI is currently being used widely in a multicenter study and has been shown to have good inter-rater reliability (N=10; r=.97). A training video has been created for the purpose of increasing reliability and validity. This is the only version of the FBI which distinguishes between MND symptoms and behavioral changes due to FTD. **Weaknesses:** This ALS version of the scale has not yet been published. It is more time consuming than the FBI-mod, which is a self-administed questionnaire given to caregivers without requiring staff involvement. **Psychometric Properties:** *Feasibility:* Easy to use interview that can be completed by phone or in person, by any trained staff person. *Reliability:* The original FBI has high inter-rater reliability (Cohen's kappa of .90) and item consistency (a Cronbach alpha of .89). The FBI-ALS version also has high interrater reliability (r=.986; N=10). *Validity:* Using the original FBI, discriminant function correctly classified 92.7% versus all other patients (vascular dementia (VaD), Alzheimer's disease (AD), primary progressive aphasia (PPA), and depressive disorder (DD) patients.) The mean scores of FLD patients were significantly above all other groups. ***Sensitivity to Change:*** The FBI has been shown to be sensitive to changes in behavior and personality in both the frontal variant and PPA variants of FTD (Marczinski CA, et al.) **Relationships to other variables:** This measures a behavioral construct distinct from clinical depression, PBA, and neuropsychological function (e.g. executive dysfunction). **Availability:** Publicly available, no copyright. This version has been completed with permission from the FBI originator, Andrew Kertesz. **Purpose of Tool:** Screening tool. **Used in:** The original FBI has been used widely in clinical trials and observational studies. This ALS-specific version is currently being used widely in a multicenter study (Oxidative Stress Study being conducted by Hiroshi Mitsumoto). **Administration time:** 15-30 minutes

Description of FBI-Mod-Heidler-Gary for
ALS Common Data Elements

Instrument Name:	Frontal Behavioral Inventory-Mod (FBI-Mod)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured : FTD-Type Behavioral and Personality Change** **Generic vs. disease specific:** Specific with regards to FTD-type dementia, but generic with regards to the presence of MND **Means of administration**: Caregiver self-administered interview. This self-administered questionnaire distinguishes it from the staff-led interview method used with the traditional FBI. **Intended respondent** (e.g. patient, caregiver, etc): Caregiver **# of items:** 24 items **# of subscales and names of sub-scales:** Two subscales: Negative Score, and Disinhibition Score **# of items per sub-scale:** 12 each
Comments/Special instructions:	**Scoring:** Items are scored according to the extent of the behavioral change: 0 = None/never; 1 = Mild, occasional; 2 = Moderate/often; 3 = Severe, most of the time. **Background:** The FBI-Mod is unique in two ways as compared with the original FBI: 1) Items are simplified to ask only one question per item, as opposed to two questions, and 2) the test is completed by the caregiver themselves as opposed to being completed as a staff-led interview.
References:	**Key Reference:** Heidler-Gary, J & Hillis, A (2007). Distinctions between the dementia in Amyotrophic Lateral Sclerosis with Frontotemporal Dementia and the dementia of Alzheimer's disease. Amyotrophic Lateral Sclerosis, 8, 276-282. Kertesz, A., Davidson, W., & Fox, H. (1997). Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. Can J Neurol Sci, 24(1), 29-36. **Other References:** Kertesz, A. (1998). The quantification of behavior in frontal lobe dementia. In A. Kertesz & D. G. Munoz (Eds.), Pick's disease and Pick complex (pp. 47-67). New York: Wiley & Sons, Inc. Kertesz, A., Nadkarni, N., Davidson, W., & Thomas, A. W. (2000). The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. Journal of the International Neuropsychological Society, 6(4), 460-468.
Rationale/ Justification:	**Strengths:** Simplified, shorter administration time. One study found good validity when using it to distinguish between AD and FTD. Not copyrighted.

	Weaknesses: Not ALS specific. At least 15 items have overlap with MND symptoms, making it difficult to disentangle MND changes from behavioral changes due to frontotemporal deterioration. Because the caregiver is answering the questions without a staff member present, there may be reduced validity due to potential misinterpretation of items by a caregiver unfamiliar with complex nature of the personality/behavior constructs, and unaware of how the MND symptoms play a role in behavior. **Psychometric Properties:** *Feasibility:* Easy to use because no staff are required. *Reliability:* No tests of reliability have been completed for this version of the FBI. *Validity:* In a study comparing AD with ALS-FTD patients, ALS-FTD patients were reported as having significantly more total behavioral problems and more negative behaviors in particular (F=6.5 p=.01). No study to date has tested the validity of this instrument on ALS-normals vs ALS-FTD. **Sensitivity to Change:** Not yet studied. **Relationships to other variables:** This measures a behavioral construct distinct from clinical depression, PBA, and neuropsychological function (e.g. executive dysfunction). **Availability:** Publicly available, no copyright. **Purpose of Tool:** Screening tool. **Used in:** This version of the FBI has been used in one study only. The original FBI, conducted as a staff-led interview, has been used extensively in the field. **Administration time:** 10 minutes

Description of FBI for
ALS Common Data Elements

Instrument Name:	Frontal Behavioral Inventory (FBI)
Classification:	**Classification**: Core
Short Description of Instrument:	**Construct measured :** FTD-Type Behavioral and Personality Change **Generic vs. disease specific:** Specific with regards to FTD dementia, but generic with regards to the presence of MND **Means of administration**: Caregiver interview by research staff, by phone or in person, without patient present **Intended respondent**: Caregiver **# of items:** 24 **# of subscales and names of sub-scales:** Two subscales: Negative Behavior and Disinhibition **# of items per sub-scale:** 12 each
Comments/Special instructions:	**Scoring:** Items are scored according to the extent of the behavioral change: 0 = None/never; 1 = Mild, occasional; 2 = Moderate/often; 3 = Severe, most of the time. **Background:** This original version of the FBI has one or two questions for each item, to clarify the question, and it is conducted as a staff-led interview. It does not distinguish between MND symptoms and behavioral changes due to FTD.
References:	**Key Reference:** Kertesz, A., Davidson, W., & Fox, H. (1997). Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. Can J Neurol Sci, 24(1), 29-36. **Other References:** Kertesz, A. (1998). The quantification of behavior in frontal lobe dementia. In A. Kertesz & D. G. Munoz (Eds.), Pick's disease and Pick complex (pp. 47-67). New York: Wiley & Sons, Inc. Kertesz, A., Nadkarni, N., Davidson, W., & Thomas, A. W. (2000). The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. Journal of the International Neuropsychological Society, 6(4), 460-468. Kertesz, A., Davidson, W., McCabe, P., & Munoz, D. (2003). Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. Alzheimer Disease & Associated Disorders, 17(4), 223-229. Marczinski, C. A., Davidson, W., & Kertesz, A. (2004). A longitudinal study of behavior in frontotemporal dementia and primary progressive aphasia. Cogn Behav Neurol, 17(4), 185-190.

Description of FBI for
ALS Common Data Elements

Rationale/ Justification:	**Strengths:** Good reliability and validity. Widely used. Not copyrighted. **Weaknesses:** Not ALS specific. At least 15 items have overlap with MND symptoms, making it difficult to disentangle MND changes from behavioral changes due to frontotemporal deterioration. It is more time consuming than the FBI-mod, which is a self-administed questionnaire given to caregivers without requiring staff involvement. **Psychometric Properties:** *Feasibility:* Easy to use interview that can be completed by phone or in person, by any trained staff person. *Reliability:* High interrater reliability (Cohen's kappa of .90) and item consistency (a Cronbach alpha of .89). *Validity:* Discriminant function correctly classified 92.7% versus other patients (vascular dementia (VaD), Alzheimer's disease (AD), primary progressive aphasia (PPA), and depressive disorder (DD) patients.) The mean scores of FLD patients were significantly above all other groups. ***Sensitivity to Change:*** The FBI has been shown to be sensitive to changes in behavior and personality in both the frontal variant and PPA variants of FTD (Marczinski et al.) **Relationships to other variables:** This measures a behavioral construct distinct from clinical depression, PBA, and neuropsychological function (e.g. executive dysfunction). **Availability:** Copyright belongs to Andrew Kertesz. **Purpose of Tool:** Screening tool. **Used in:** This tool has been used widely in clinical trials and observational studies. **Administration time:** 15-25 minutes

Description of FRSBe™ for
ALS Common Data Elements

Instrument Name:	Frontal Systems Behavior Scale™ (FrSBe™)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured**: This scale assesses behavior related to frontal systems damage. It also quantifies behavioral changes over time by including both baseline (retrospective) and current assessments of behavior. Forms are available for both patient and family member to complete, with separate norms for each informant. **Generic vs. disease specific**: Generic **Means of administration:** Paper and pencil **Intended respondent**: Patient and/or caregiver **# of items**: 46 items **# of subscales and names of sub-scales:** 3 – Apathy, Disinhibition, Executive Dysfunction **# of items per sub-scale:** Apathy (14 items), Disinhibition (15 items), Executive Dysfunction (17 items)
Comments/Special instructions:	**Scoring:** Each item is rated on a 5-point Likert scale. Totals are generated for each subscale and normative data is referenced (based on patient gender, age and education) and standardized T scores are determined (mean: 50, SD:10). Interpretation of results require training and coursework in psychological assessment. **Background:** Formerly the Frontal Lobe Personality Scale (FLOPS), the FrSBe was designed to identify and quantify behavioral problems associated with frontal lobe dysfunction.
References:	**Key Reference:** Grace J, Malloy PF. Frontal Systems Behavior Scale Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc. 2001. **Other References:** Grossman, AB, Woolley-Levine, S, Bradley, WG, Miller, RG. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis*. 2007; 8: 56-61.
Rationale/ Justification:	**Strengths:** Assesses multiple domains of frontal lobe functioning and allows for comparison of premorbid behavior with current status. Also allows for comparison between patient and caregiver reports. **Weaknesses:** Possible exaggeration of symptoms due to the motor component, particurly the apathy scale. Scoring requires normative database and understanding of T scores. **Psychometric Properties:** *Feasibility:* Informants completing the Family Rating Form should have at least weekly contact with the patient to ensure accurate behavioral observation.

	Patients must have cognitive capacity to read and complete the form. *Reliability:* Acceptable based on normative sample data (Grace). *Validity:* Convergent validity with other behavioral measures was high (NPI, r=.64). Discriminant validity also good (Grace). Construct validity also reviewed in manual and acceptable. **Sensitivity to Change:** This measure was designed in part to assess change over time. **Relationships to other variables:** In ALS patients (Grossman), Apathy scores correlated with verbal fluency, and bulbar-onset patients had higher Apathy scores than limb-onset. The severity of bulbar dysfunction was not associated with Apathy scores. FrSBe ratings were not correlated with FVC, ALSFRS-R, symptom duration or BDI-II scores in this study. In non-ALS studies, Apathy and Executive Dysfunction subscale scores are correlated with IADL's (Grace), and the Disinhibition scale score is strongly related to caregiver burden (Grace). **Availability:** Through Psychological Assessment Resources, Inc. This measure is copyrighted and cannot be reproduced without permission. http://www4.parinc.com/Products/Product.aspx?ProductID=FRSBE **Purpose of Tool:** Screening **Used in:** Observational studies **Administration time:** The scale takes 10 minutes to administer and 10-15 minutes to score.

Description of GDS for
ALS Common Data Elements

Instrument Name:	Geriatric Depression Scale (GDS)
Classification:	**Classification**: Exploratory
Short Description of Instrument:	**Construct measured:** Depression in geriatric patients. **Generic vs. disease specific :** Generic **Means of administration:** Self-report **Intended respondent**: Patient **# of items**: 30 **# of subscales and names of sub-scales:** N/A (total score) **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** One point is given for each of these answers: 1. No; 2. Yes; 3. Yes; 4. Yes; 5. No; 6. Yes; 7. No; 8. Yes; 9. No; 10 Yes; 11. Yes; 12. Yes; 13. Yes; 14. Yes; 15. No; 16. Yes; 17. Yes; 18. Yes; 19. No; 20. Yes; 21. No; 26. Yes; 27. No; 28. Yes; 29. No; 30. No. A score of 0-9 is considered normal; 10-19 indicates mild depression; and a score of over 20 is suggestive of severe depression. **Background:** Developed to screen for depression without notable focus on somatic symptoms. Items were geared to assess psychological symptoms and cognitive complaints associated with depression. The measure's simplicity was also designed to limit resistance towards psychiatric assessment or intervention by older adults.
References:	**Key Reference:** Brink TL, Yesavage JA, Lum O, Heersema P, Adey MB, Rose TL: Screening tests for geriatric depression. *Clinical Gerontologist 1:* 37-44, 1982. **Other References:** Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, Leirer VO: Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research 17:* 37-49, 1983. Sheikh JI, Yesavage JA: Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontology: A Guide to Assessment and Intervention 165-173, NY: The Haworth Press, 1986. Sheikh JI, Yesavage JA, Brooks JO, III, Friedman LF, Gratzinger P, Hill RD, Zadeik A, Crook T: Proposed factor structure of the Geriatric Depression Scale. *International Psychogeriatrics 3:* 23-28, 1991.

Description of GDS for
ALS Common Data Elements

Rationale/ Justification:	**Strengths:** Quick, easy to use, completed by patient, does not require interview or informant, can be completed verbally or in writing. **Weaknesses:** Not appropriate for younger adult patient population (normed on patients 55 and older), cut off scores do not categorize patients into moderate range, just mild and severe. **Psychometric Properties:** *Feasibility:* Easy to administer, quick to score. *Reliability:* Test-retest reliability (1 week) 0.85. Internal consistency (alpha coefficient 0.94) higher than other depression measures (Hamilton Depression Rating Scale, Zung Self-Rating Depression Scale), Split-half reliability (0.94). *Validity:* Cut-off scores of 11 have 84% sensitivity and 95% specificity; cut-off of 14 decreases sensitivity to 80% but increases specificity to 100%. **Sensitivity to Change:** Unknown **Relationships to other variables:** Initial studies suggested it has validity with both physically healthy and physically ill elderly adults. **Availability:** Free, in the public domain, there are 34 language versions available online (Stanford.edu). **Purpose of Tool:** Screening **Used in:** Not routinely used in ALS trials **Administration time:** 5 minutes

Description of Hamilton Depression Rating Scale for ALS Common Data Elements

Instrument Name:	Hamilton Depression Rating Scale (HAM-D)
Classification:	**Classification** : Exploratory
Short Description of Instrument:	**Construct measured:** This rater-administered instrument is the most widely used rating scale in depression research. There are semi-structured versions available. It is in the public domain and available in many languages. **Generic vs. disease specific :** Generic **Means of administration:** Semi-structured interview completed by trained interviewer **Intended respondent**: Patient **# of items :** 17 items **# of subscales and names of sub-scales** : N/A **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** Scores range from 0 – 54, with higher scores indicating increasing severity of depression. Scoring completed by trained interviewer. **Background:** This measure is considered the gold standard in depression research and is widely used. It is common in antidepressant drug trials but is not systematically used in ALS trials.
References:	**Key Reference:** Hamilton M. Hamilton Depression Scale. In, ECDEU Assessment Manual for Psychopharmacology, Revised Edition (ed. W Guy), pp. 179-192, 1976. Rockville, Maryland: National Institute of Mental Health. **Other References:** Hamilton, M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6:278-96, 1967. Santen, G. Sensitivity of the individual items of the Hamilton depression rating scale to response and its consequences for the assessment of efficacy. -*J Psychiatr Res*, 42(12): 1000-9, 2008.
Rationale/ Justification:	**Strengths:** Widely used, items somewhat consistent with diagnostic criteria for Major Depressive Disorder, considered the gold standard in antidepressant trials for diagnosis of depression. **Weaknesses:** There are no publications on use of this scale in ALS studies. Several items assess somatic symptoms (psychomotor retardation, anxiety: somatic, somatic: GI, somatic: general, genital symptoms, hypochondriasis, loss of weight) which may result in over-diagnosis of depression **Psychometric Properties:**

Description of Hamilton Depression Rating Scale for ALS Common Data Elements

	Feasibility: Low feasibility, requires trained interviewer and 20-30 minutes of interview. *Reliability:* Less than optimal since completed by interviewer which may result in variability. *Validity:* As sensitive to detecting effect size in clinical trials as Montgomery-Asberg Depression Rating Scale and Clinical Impressions Rating Scale **Sensitivity to Change:** Santen found that not all items of the HAM-D are equally sensitive to detect responding patients in a clinical trial. **Relationships to other variables:** **Availability:** Appears to be in the public domain. **Purpose of Tool:** Diagnostic **Used in:** Clinical trials (Avenir study) **Administration time:** 20-30 minutes

Description of HADS for
ALS Common Data Elements

Instrument Name:	Hospital Anxiety and Depression Scale (HADS)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured**: This scale assesses anxiety and depression in general hospital patients. **Generic vs. disease specific**: Generic **Means of administration:** Self- administered **Intended respondent**: patient **# of items:** 14 items **# of subscales and names of sub-scales**: 2 subscales: Anxiety, Depression **# of items per sub-scale**: Anxiety (7 items), Depression (7 items)
Comments/Special instructions:	**Scoring:** Items are rated on a 4-point Likert-type scale ranging from 0 to 3, generating a scale range of 0 to 42 points, with higher scores representing greater symptom severity. The anxiety subscale has 3 items that refer to panic and 4 to generalized anxiety. Add the A questions to get a score for anxiety and the D questions for depression. Scores of 0-7 indicate normal levels of anxiety and depression; 8-10 indicate borderline abnormal anxiety and depression levels and 11-21 suggest abnormal levels of anxiety and depression. **Background:** The HADS is a 14-item self-report scale that consists of a depression and an anxiety scale, each with 7 items. The scale was designed to screen for mood disorders in general (non-psychiatric) medical outpatients. It focuses on subjective disturbances of mood rather than physical signs, and aims at distinguishing depression from anxiety. Compared to other instruments scales, it focuses on emotional aspects of anxiety disturbances, as opposed to somatic and cognitive symptoms.
References:	**Key Reference:** Zigmond AS and Snaith RP: The Hospital Anxiety And Depression Scale *Acta Psychiatr Scand* 1983, 67:361-70. **Other References:** Ferentinos P, Paparrigopoulos T, Rentzos M, Zouvelou V, Alexakis T, Evdokimdis I. Prevalence of major depression in ALS; Comparison of a semi-structured interview and four self- report measures. Amyotrophic Lateral Sclerosis 2011; Early online 1-6 Wicks P, Abrahams S, Masi D, Hejda-Forde S, Leigh PN, Goldstein LH Prevalence of depression in a 12-month consecutive sample of patients with ALS. Eur J.Neurol 2007; 14:993-1001

	Goldstein LH, Adamson M, Jeffrey L, Down K, Barby T, Wilson C, Leigh PN The psychological impact of MND on patients and carers. J Neurol Sci 1998; 160(Suppl1) S114-121 Goldstein LH, Atkins L, Landau S, Brown RG, Leigh PN. Longitudinal predictors of psychological distress and self-esteem in people with ALS. Neurology 2006; 67:1652-1658 Olsson AG, Markhede I, Strang S, Persson LI. Differences in quality of life modalities give rise to needs of individual support in patients with ALS and their next of kin. Palliative and Supportive Care 2010; 8:75-82 Crawford, J. R., Henry, J. D., Crombie, C. & Taylor, E. P. Normative data for the HADS from a large non-clinical sample. British Journal of Clinical Psychology 2001; 40: 429–434.
Rationale/ Justification:	**Strengths:** Serves as a good screening measure. Has been widely used. Over 80 translations available **Weaknesses:** This scale is not designed for ALS; however, it is a quick screen. A number of studies in ALS have removed the item "I feel as if I am slowed down" from the Depression subscale but formal validation of this approach is awaited (Abrahams et al. 1997). Requires insight to provide accurate reflection. No proxy verification. **Psychometric Properties:** *Feasibility:* Relatively simple to complete. *Reliability:* Internal consistency described for patients with cancer (Moorey et al 1991): Anxiety subscale Cronbach's alpha = 0.93; Depression subscale alpha= 0.9. In healthy UK sample, internal consistency for Anxiety, Depression and Total scores were 0.82, 0.77 and 0.86 respectively (Crawford et al 2001). Test-retest reliability for healthy sample: correlation for Depression scale= 0.92; Anxiety subscale 0.89 (Snaith & Zigmond, test manual) *Validity*: Concurrent validity established in a number of studies (see Snaith & Zigmond, test manual). Depression scores correlate with other measures of depression in ALS (Ferentinos et al 2011) **Sensitivity to Change:** HADS scores may not change over time in ALS groups (Goldstein et al 2006; Olsson et al 2010) **Relationships to other variables: Examples:** HADS depression scores differentiate between patients taking/ not taking antidepressants, and male patients and older patents at time of diagnosis had higher HADS depression scores; HADS anxiety scores differentiated between patients with and without a psychiatric history and those taking/ not taking antidepressants (Wicks et al 2007). HADS Depression scores correlated with limb impairment, overall disease severity scores and, also with

	Anxiety scores with impairment on domains of the Sickness Impact Scale (Goldstein et al 1998). Anxiety and depression subscale scores correlated with subscales of the Sickness Impact Scale; Depression subscale scores correlated with speech and mobility scores on the Barthel Index and Anxiety scores correlated with Barthel speech items (Hogg et al 1994). **Availability:** http://shop.gl-assessment.co.uk/home.php?cat=417 **Purpose of Tool:** Screening **Used in** : clinical trials, observational studies **Administration time:** The scale only takes about 2-5 minutes to complete.

Description of NPI Clinician rating Scale (NPI-C) for ALS Common Data Elements

Instrument Name:	Neuropsychiatric Inventory-Clinician rating Scale (NPI-C)
Classification:	**Classification**: Exploratory
Short Description of Instrument:	**Construct measured**: Psychopathology in dementia **Generic vs. disease specific:** Generic **Means of administration:** Caregiver self-report form **Intended respondent**: Caregiver **# of items**: 14 domains measured, with varying numbers of questions to measure them **# of subscales and names of sub-scales:** No subscales **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** The NPI-C includes 2 domains not included in the NPI. Scoring for the NPI-C was revised to measure an additional 2 domains, based upon prevalence data suggesting that agitation and anger should be separated into two distinct categories, and adding "aberrant vocalization" to the domain list. **Background:** The NPI-C uses more specific ratings for each item within a domain, allowing for ratings for frequency, severity and distress to be calculated individually and summed to create a total domain score. This scoring system allows for more sensitivity, to track symptom change across time. The NPI-C involves the adoption of an expert clinical rating system using a "LEAD" standard (longitudinal data, expert rater, all data). Using this system, the rater interviews the caregiver (as in the original NPI), then interviews the patient, to compare caregiver insights with patient's perceptions. The clinician uses additional data, including chart reviews and other caregiver interviews, interpreting these data using clinical judgment. The NPI-C is translated into French, Greek, Hungarian, Italian, Portuguese, and Spanish, to facilitate international collaboration.
References:	**Key Reference:** K de Medeiros, P. Robert et al. for the MPI-C Research Group. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. *International Psychogeriatics* 2010, 22:6, 984-994. **Other References:** Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez O, DeKosky ST. Validation of the NPI-Q, a Brief Clinical Form of the Neuropsychiatric Inventory: *J Neuropsychiatry Clin Neurosci* 2000; 12:2.

Description of NPI Clinician rating Scale (NPI-C) for ALS Common Data Elements

Rationale/ Justification:	**Strengths:** This scale allows expert clinicians to incorporate data from all sources, generating better validity by reducing caregiver bias. It has been widely translated, making it a likely tool to be used in multi-center clinical trials. **Weaknesses:** Caregiver ratings can be biased due to misinterpretation of complex clinical syndromes that are not in the common lexicon (e.g. .delusions, hallucinations, apathy). The measure does not specifically adjust for motor neuron disease, so the confounds of motor weakness, dysarthria, and fatigue complicate item ratings. More staff resources are used with the NPI-C because of the expert rater (LEAD) system. Copyright fees will likely apply for funded research projects. **Psychometric Properties:** *Feasibility:* The measure is rather simple to administer, instructing caregivers to rate each domain. Interviews are then conducted with patients and chart reviews are conducted. *Reliability:* Inter-rater reliability was generally strong to moderate. *Validity:* Correlations for all NPI-C domains were moderate to strong, when convergent validity was tested with outside measures. **Sensitivity to Change:** Unknown. **Relationships to other variables:** Unknown. **Availability/Copyright Fees:** Non- funded academic research: if the project is not explicitly funded, but funding comes from overall departmental funds, from the University or individual funds then fees are waived. Funded academic research, including projects receiving funding from commerce, government, EU, and commercial studies (industry, CRO, any for-profit companies) should contact Dr. Cummings via MAPI Research Trust, to negotiate fees. http://www.mapitrust.org/services/questionnairelicensing/cataloguequestionnaires/71-npi **Purpose of Tool:** Screening **Used in:** This recently developed tool has not yet been used in clinical trials. **Administration time:** 10-45 minutes.

Description of NPI-Questionnaire version for
ALS Common Data Elements

Instrument Name:	Neuropsychiatric Inventory-Questionnaire version (NPI-Q)
Classification:	**Classification**: Supplementary
Short Description of Instrument:	**Construct measured**: Pathology in dementia **Generic vs. disease specific:** Generic **Means of administration:** Caregiver self-report form **Intended respondent**: Caregiver **# of items**: 12 items **# of subscales and names of sub-scales:** N/A **# of items per sub-scale:** 12
Comments/Special instructions:	**Scoring:** Each of the 12 domains is rated by severity (1-3). The symptom frequency that is measured in the original NPI is not included in this version of the NPI-Q. The total score reflects the total sum of the individual severity scores (ranging from 0-36). Caregiver distress level is also rated (0 = not distressing at all, to 5 = extremely distressing), with a total distress score reflecting the total sum of the individual severity scores (ranging from 0-60). **Background:** The NPI-Q is a shortened, revised version of the NPI which replaces the interview with a caregiver self-report form, includes shortened screening questions, and rates only severity and distress for each symptom, removing the frequency rating. The same 12 neuropsychiatric domains are included, as in the original NPI: (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbance, and appetite/eating disturbances.)
References:	**Key Reference:** Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez O, DeKosky ST. Validation of the NPI-Q, a Brief Clinical Form of the Neuropsychiatric Inventory: *J Neuropsychiatry Clin Neurosci* 2000; 12:2. **Other References:**
Rationale/ Justification:	**Strengths:** This scale has been widely used across many neurological disorders, allowing for comparisons. The NPI-Q is very brief, and uses no staff resources to administer. **Weaknesses:** Caregiver ratings can be biased due to misinterpretation of complex clinical syndromes that are not in the common lexicon (e.g. .delusions, hallucinations, apathy). Domains are weighted towards moderate stage dementia and less relevant for early-stage changes. Low NPI-Q validity ratings were found for patients with high MMSE scores. Ratings are acquired via caregivers instead of patients or clinicians, and is therefore less sensitive to

change, due to recall bias, cultural beliefs, caregiver mood, etc. The NPI-Q is not designed for the ALS population, thus making dysarthria, motor weakness, and fatigue confounds in a variety of items. Copyright fees will likely apply for funded research projects.

Psychometric Properties:

Feasibility: The interview is rather simple to administer, taking 5 minutes to complete.

Reliability: Test-retest correlations for symptom and distress scores was adequate (.80 and .94 respectively). Strong interscale correlations existed between the NPI total score and the NPI-Q severity total (.91), and distress total score (.92).

Validity: The NPI was valid when compared with scores on the MMSE, only for those patients with low MMSE scores (r=.44).

Sensitivity to Change: Unknown.

Relationships to other variables: The NPI-Q has limited correlation with cognitive functioning, as measured by the MMSE, particularly for patients who are only mildly impaired. It has a stronger correlation with cognitive performance, for those with moderate to severe stage cognitive decline. Its relationship to depression and other measures are unknown.

Availability/Copyright Fees: Non- funded academic research: if the project is not explicitly funded, but funding comes from overall departmental funds, from the University or individual funds then fees are waived. Funded academic research, including projects receiving funding from commerce, government, EU, and commercial studies (industry, CRO, any for-profit companies) should contact Dr. Cummings via MAPI Research Trust, to negotiate fees.

Purpose of Tool: Screening

Used in: Used in a variety of clinical trials, as a dependent measure of behavior and personality change.

Administration time: 5 minutes

Description of NPI for
ALS Common Data Elements

Instrument Name:	Neuropsychiatric Inventory (NPI)
Classification:	**Classification**: Supplemental
Short Description of Instrument:	**Construct measured**: Psychopathology in dementia **Generic vs. disease specific:** Generic **Means of administration:** Interview by trained staff member **Intended respondent**: Caregiver **# of items**: 12 domains **# of subscales and names of sub-scales:** No subscales **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** Each of the 12 domains are rated by frequency (1-4) and severity (1-3-3), and total scores are calculated by multiplying frequency x severity. A global score is a sum of all 12 total scores, indicating a composite score of all problem areas. Caregiver distress is also measured. **Background:** Using scripted questions, the caregiver is asked whether the patient's behavior has changed after the onset of the dementia. If the initial screening question is endorsed positively, the seven or eight follow up questions are asked. The NPI's ten domains include: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, sleep problems, and appetite/eating problems.
References:	**Key Reference:** Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44:2308-2314. **Other References:**
Rationale/ Justification:	**Strengths:** This scale has been widely used across many neurological disorders, allowing for comparisons. Ratings that combine severity and frequency are useful, and not found in other measures. The NPI can be brief and easy to use, taking approximately ten minutes for those patients with less pathology. **Weaknesses:** Staff time spent completing the interview requires resources, particularly for patients with higher levels of pathology. Symptom domains are weighted towards moderate stage dementia and less relevant for early-stage changes. Ratings are acquired via caregivers instead of patients or clinicians, and is therefore less sensitive to change, due to recall bias, cultural beliefs, caregiver mood, etc. Copyright fees will likely be charged for funded projects.

Psychometric Properties:

Feasibility: The interview is rather simple to administer, taking 7-10 minutes for patients with few symptoms, or 30 or more minutes for more impaired patients.

Reliability: Inter-rater reliability is strong, ranging from 96%-100% between rater agreement for frequency and 89%-100% between rater agreement for severity.

Validity: Concurrent validity was significant at the p<.01 level, demonstrating that the NPI indentified pathology similarly to the HDRS and the BEHAVE-AD.

Sensitivity to Change: Test-retest reliability was high (.79 for frequency and .86 for severity), indicating that the measure may be a sensitive indicator of change (yet no explicit test of change sensitivity is known).

Relationships to other variables: The NPI intentionally avoids questions about vegetative symptoms of depression, avoiding the confounding effects of overlapping symptoms of dementia and depression.

Availability/Copyright Fees: Non- funded academic research: if the project is not explicitly funded, but funding comes from overall departmental funds, from the University or individual funds then fees are waived. Funded academic research, including projects receiving funding from commerce, government, EU, and commercial studies (industry, CRO, any for-profit companies) should contact Dr. Cummings via MAPI Research Trust, to negotiate fees.

http://www.mapitrust.org/services/questionnairelicensing/cataloguequestionnaires/71-npi

Purpose of Tool: Screening

Used in: Used in a variety of clinical trials, as a dependent measure of behavior and personality change.

Administration time: 7-10 minutes for patients with few symptoms, or 30 minutes for more impaired patients.

Description of PSSFTS for
ALS Common Data Elements

Instrument Name:	Penn State Brief Exam of Frontal and Temporal Dysfunction Syndromes (PSFTS)
Classification:	**Classification**: Core
Short Description of Instrument:	**Construct measured:** Letter fluency, judgment, attention, repetition, category fluency, similarities, reading comprehension, constructional praxis, naming, orientation, mental calculations, premorbid intelligence, and behavior. **Generic vs. disease specific:** FTD specific and tailored for ALS. Administration is controlled for motor weakness and allows for spoken or written word responses to verbal measures. **Means of administration:** By trained personnel, usually a nurse or other non-neuropsychologist trained to administer. **Intended respondent**: Patient except for the FBI, which is administered to the caregiver. **# of items :** Multiple sub-parts as listed below, many with several items. **# of subscales and names of sub-scales** : There are 6 subscales: 1. Letter Fluency (http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8091-108&Mode=summary). 2. Category Fluency (http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8091-108&Mode=summary). 3. National Adult Reading Test (NART) to assess premorbid intelligence (IQ) for those with sufficient intelligibility of speech (http://www.commondataelements.ninds.nih.gov/CRFdetail.aspx?FormId=1031) . 4. Neurobehavioral Cognitive Status Examination (COGNISTAT) to assess reasoning (similarities, judgment), attention span, language (repetition, auditory comprehension, naming), 2-D constructional skills, mental calculations, orientation, and verbal memory. (http://www.cognistat.com/). 5. Reading comprehension via the Boston Diagnostic Aphasia Exam (BDAE) Oral Reading and Reading Comprehension – Short Form for those with sufficient intelligibility of speech (5 items) (http://www.proedinc.com/customer/ProductView.aspx?ID=3399&sSearchWord=Boston++Diagnostic+Aphasia+Exam). 6. Frontal Behavioral Inventory (FBI)is given concurrently to the caregiver to assess for behavioral changes (http://www.commondataelements.ninds.nih.gov/CRFdetail.aspx?FormId=1105). **# of items per sub-scale:** Varies. See listing above.

Comments/Special instructions:	**Scoring:** Letter Fluency and Category Fluency are assessed and scored as per Gladsjo et al (Gladsjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: Demographic corrections for age, education and ethnicity. Assessment 1999; 6: 147-178.). For those with motor weakness, a fluency ratio is used as per Abrahams et al (Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein YH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis. Neuropsychologia 2000;38:734-747.). NART, COGNISAT and BDAE per published guidelines: FBI consists of 24 questions, each scored 0-3, with 3 indicating the highest level of frontal dysfunction. Scores range from 0 (normal) to 72 (behavior consistent with severe frontotemporal dementia). A score of 27 or higher is considered to be consistent with frontal lobe dementia. Kertesz A, Davidson W and Fox H. Frontal Behavioral Inventory: Diagnostic critertia for Frontal Lobe Dementia. The Canadian Journal of Neurological Sciences 1997,24(1):29-35. **Background:** Piloted in a large multidisciplinary ALS clinic. Now undergoing use by multiple sites in the US via collaboration with Penn State. 145 subjects enrolled so far in this multicenter study. One publication on regional and gender differences has been accepted for the June 2012 issue of Neurodegen Dis Manag.
References:	**Key Reference:** Flaherty-Craig C, Eslinger P, Stephens B, Simmons Z. A rapid screening battery to identify frontal dysfunction in patients with ALS. Neuro. 2006; 67: 2070-2. **Other References:** Flaherty-Craig C, Brothers A, Dearman B, Eslinger P, Simmons Z. Penn State screen exam for the detection of frontal and temporal dysfunction syndromes: application to ALS. Amyotr Lat Scler 2009; 10: 107-112. Flaherty-Craig C, Brothers A, Yang C, Svoboda R, Simmons Z. Declines in problem solving and anosognosia in Amyotrophic Lateral Sclerosis: Application of Guilford's Structure of Intellect Theory. Cogn Behav Neuro 24(1) March,2011.
Rationale/ Justification:	**Strengths:** 1) ALS-tailored 2) More information than very brief (5 minute) screens 3) modifications available for motor weakness 4) relatively quick to administer 5) published material available with ALS patients to support its use 6) FBI can be administered to caregiver while PSFTS is being administered to patient 7) has been used successfully in a large multidisciplinary ALS clinic 8) is now undergoing use at multiple sites in the USA. **Weaknesses:** 1) At 20 minutes for administration, this is longer than some brief exams 2) cannot be self-administered 3) some parts (NART and BDAE) not administered to those with insufficient intelligibility of speech 4) scoring requires multiple normative databases. **Psychometric Properties:** *Feasibility:* Able to be administered in a large multidisciplinary ALS clinic.

	Reliability: Good studies for component parts. *Validity:* No validity studies on overall instrument for use in ALS. Excellent validity studies available for component parts. **Sensitivity to Change:** Not assessed for overall instrument. **Relationships to other variables:** Strong sensitivity and specificity when compared to comprehensive neuropsychological test battery. **Availability:** Some parts are copyright-protected: COGNISTAT, BDAE-SF **Purpose of Tool:** Initial cognitive behavioral assessment for treatment planning **Used in**: Multidisciplinary ALS clinics, non-ALS dementia clinic and ALS multi-center national study in USA. **Administration time:** 20 minutes

Description of UCSF Screening Exam for
ALS Common Data Elements

Instrument Name:	UCSF Screening Exam
Classification:	**Classification** : Core
Short Description of Instrument:	**Construct measured**: Cognitive and behavioral changes, depression level, and presence of pseudobulbar affect. **Generic vs. disease specific**: Specific to both ALS and FTD dementia, tailored to the overlap syndrome of ALS-FTD. **Means of administration**: The verbal fluency test is administered by staff to the patient, and the FBI-ALS interview is given by staff to the caregiver, in person or by phone. The BDII and CNS-LS are self-report questionnaires given to the patient. The ALS-CBS (described in detail in its own CDE document) is administered by a staff member to the patient and caregiver. **Intended respondent**: The FBI-ALS interview is given to the caregiver, in person or by phone, and the verbal fluency, depression, and PBA measures are given to the patient. The ALS-CBS has both a patient and caregiver section. **# of items**: The written verbal fluency has two tests: C words and S words, the FBI-ALS has 24 items, the CNS-LS has 7 items, the BDII has 21 items (each detailed in their respective templates). The ALS-CBS is composed of 8 cognitive tasks and a 15-item caregiver-rated behavioral change questionnaire. **# of subscales and names of sub-scales:** Each are detailed in their respective templates. **# of items per sub-scale:** Each are detailed in their respective templates.
Comments/Special instructions:	**Scoring:** Varies by measure, detailed in each template. **Background:** The UCSF Screening Exam consists of 5 measures, all of which are individually described in other templates. The measures include: written verbal fluency, FBI-ALS interview, Beck Depression Inventory-II, the ALS-CBS, and the CNS-LS.
References:	**Key Reference:** Each are detailed in their respective templates.
Rationale/ Justification:	**Strengths:** This battery of measures was selected to broadly screen for the components of cognitive and behavioral change in ALS, and to simultaneously identify how psuedobulbar affect and depression may complicate the syndrome. The written fluency test measures a key feature of ALSci, and is created specifically to control for motor and bulbar weakness. The FBI-ALS was created specifically to remove the effects of MND changes when measuring behavior and personality change. The depression and PBA measures are generic for those conditions, and are important to include because these syndromes can be confused with neurologically-based cognitive change and behavioral change. The ALS-CBS is included to provide a rapid screen of more broad cognitive deficits seen in ALS. By including these 5 components in the UCSF

	screen, one is able to separate out the effects of co-morbid conditions, gain a broad screen of cognitive capacity, and obtain a careful understanding of behavioral changes witnessed by caregivers. **Weaknesses:** The battery is more time consuming than a global, self report measure. No non-English translations are yet available. The ALS-FBI is yet to be validated. **Psychometric Properties:** Each measure's properties are detailed in their respective templates. *Feasibility:* Each measure's properties are detailed in their respective templates. *Reliability:* Each measure's properties are detailed in their respective templates. *Validity:* Each measure's properties are detailed in their respective templates. **Sensitivity to Change:** Each measure's properties are detailed in their respective templates. **Relationships to other variables:** Each of the tools in the battery are distinct in their measurement of the conditions that play a role in ALS-FTD. **Availability:** All are public domain with the exception of the BDII, which is copyrighted. **Purpose of Tool:** The BDII is diagnostic and the others are screening tools. **Used in:** These tools can be used in any investigation, including clinical trials. **Administration time:** Total time for the all measures: 45 minutes

Description of Written Verbal Fluency for
ALS Common Data Elements

Instrument Name:	Written Verbal Fluency Test
Classification:	**Classification**: Core
Short Description of Instrument:	**Construct measured:** This test measures rapid word generation and is dependent on executive and language functions (including generation of strategies for word search and word retrieval). **Generic vs. disease specific :** Generic **Means of administration:** Paper and pencil test **Intended respondent**: Patient **# of items :** N/A **# of subscales and names of sub-scales:** N/A **# of items per sub-scale:** N/A
Comments/Special instructions:	**Scoring:** Patient is asked to write as many words as possible beginning with the letter S in 5 mins and as many words consisting of four letters only beginning with the letter C in 4 minutes. Following a delay (which reduces fatigue), the patient is timed as they copy the words they previously generated as fast as possible, from which a Written Verbal Fluency Index is calculated. This consists of an estimate of the average time to 'think' of each word [(the time allowed for the test: 9 mins minus the time taken to copy the words), dvided by the total number of correct words]. **Background:** The test is an adaptation of the Thurstone's Word Fluency Test (Thurstone and Thurstone, 1962) which together with other spoken word fluency tests has been shown to be sensitive to frontal lobe lesions. This test was adapted to control for motor speed for use with patients with upper limb disability with the incopration of a copy condition. The test has been shown to be independent of physical disability. The test has been repeatedly shown to be sensitive to ALS.
References:	**Key Reference:** Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia 38(2000):734-747. **Other References:** Abrahams, S., Goldstein, LH., Al-Chalabi, A., Pickering, A., Morris, RG., Passingham, RE., Brooks, DJ. and Leigh PN. (1997). Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery and Psychiatry, 62, 464-472. Abrahams, S., Goldstein, L.H., Simmons, A., Brammer, M. J., Williams, S. C. R. Giampietro, V. and Leigh, P.N (2004). Word retrieval in amyotrophic lateral

	sclerosis: a functional magnetic resonance imaging study. Brain, 127, 1507 – 1517. Abrahams, S., Goldstein, L.H., Suckling, J., Ng, V., Simmons, A., Giampietro, V. Atkins, L., Williams, S.C.R. and Leigh, P.N.. (2005a) Fronto-temporal white matter changes in patients with amyotrophic lateral sclerosis. Journal of Neurology. 252, 321-331. Abrahams, S., Goldstein, L.H. and Leigh, P.N. (2005b) Cognitive change in amyotrophic lateral sclerosis: a prospective study. Neurology, 64 1222-1226
Rationale/ Justification:	**Strengths:** The adaptation to control for motor speed was designed for patients with ALS. The test has also been shown to be sensitive to frontal lobe dysfunction in ALS through functional and structural MRI studies. **Weaknesses:** Requires further validation of properties and production of normative data. The full test is not suitable for patients with marked writing difficulties. **Psychometric Properties:** *Feasibility:* The test requires that the patient can write. Spoken versions of this test can be employed in patients with severe upper limb dysfunction. *Reliability:* Has not been assessed *Validity:* The Written Verbal Fluency Index has been shown to be sensitive to frontal lobe dysfunction in ALS in functional imaging and structural imaging (Abrahams et al. 2004, 2005a.). The index has also be found to correlate with ocular fixation abnormalities in ALS (Donaghy et al. 2009) **Sensitivity to Change:** No change was reported over a 6 month period (Abrahams et al. 2005b) **Relationships to other variables:** This measure was shown not to correlate with measures of emotional lability (Palmieri et al. 2009) or measures of disease duration or disability (Abrahams et al. 2000). **Availability:** S. Abrahams, L. Goldstein. **Purpose of Tool:** Screening, research. **Used in:** Observational study. **Administration time:** 15 minutes